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Abstract

Ral small GTPases, consisting of RalA and RalB, are members of the Ras family. Their activity is upregulated by RalGEFs. Since several RalGEFs are downstream effectors of Ras, Ral is activated by the oncogenic mutant Ras. Ral is negatively regulated by RalGAP complexes that consist of a catalytic α1 or α2 subunit and its common partner β subunit and similarly regulate the activity of RalA as well as RalB *in vitro*. Ral plays an important role in the formation and progression of pancreatic and lung cancers. However, the involvement of Ral in oral squamous cell carcinoma (OSCC) is unclear. In this study, we investigated OSCC by focusing on Ral. OSCC cell lines with high Ral activation exhibited higher motility. We showed that knockdown of RalGAPβ increased the activation level of RalA and promoted the migration and invasion of HSC-2 OSCC cells *in vitro*. In contrast, overexpression of wild-type RalGAPα2 in TSU OSCC cells attenuated the activation level of RalA and inhibited cell migration and invasion. The real-time quantitative PCR analysis of samples from patients with OSCC showed that RalGAPα2 was downregulated in oral cancer tissues compared with normal epithelia. Among patients with OSCC, those with a lower expression of RalGAPα2 showed a worse overall survival rate. A comparison of DNA methylation and histone modifications of the *RalGAPα2* gene in OSCC cell lines suggested that crosstalk between DNA methylation, histone H4Ac and H3K27me2 was involved in the downregulation of RalGAPα2. Thus, activation of Ral GTPase by downregulation of RalGAP expression via a potential epigenetic mechanism may enhance OSCC progression.

Keywords: squamous cell carcinoma of head and neck, RalA protein, GTPase-activating proteins, guanine nucleotide exchange factors, DNA methylation, histone code